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TCBDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

**GASTROENTEROLOGY AND UROLOGY DEVICES PANEL**

**OF THE**

**MEDICAL DEVICES ADVISORY COMMITTEE**

**OPEN SESSION**

Thursday, July 29, 1999

8:48 a.m.

Conference Rooms G and H
Parklawn Building
5600 Fishers Lane
Rockville, Maryland

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Craig F. Donatucci, M.D.
Jenelle E. Foote, M.D.
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Joseph H. Steinbach, Ph.D.
Leonard L. Vertuno, M.D.

CONSULTANTS, TEMPORARY VOTING MEMBERS

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Naida Brooks Kalloo, M.D.
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Diane K. Newman, RNC, MSN, CRNP, FAAN

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Alan H. Bennett, M.D.

FDA

David Segerson

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

DR. A. KALLOO: Just to let you know we are waiting on some of the panel members to get here. We still don't quite have a quorum to proceed. So, as soon as they arrive, we will begin the meeting.

[Pause.]

DR. A. KALLOO: May I have your attention, please. Either because of weather or transportation difficulties, we are still waiting on one or two members to arrive. So, the plan is to reconvene at 9:15.

[Recess.]

DR. A. KALLOO: Good morning again. I think we will proceed with this morning's session.

I would like to call to order this meeting of the Gastroenterology and Urology Devices Panel. I would to note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14.

**Introductions**

Would each member introduce himself or herself, designate specialty, position title and institution and status on the panel, voting member or consultant, starting on my immediate right.

MS. CORNELIUS: I am Mary Cornelius and I am the Executive Secretary of this panel.

DR. DONATUCCI: Craig Donatucci. I am Associate

Professor of Urology at Duke University.

DR. N. KALLOO: Naida Kalloo. I am Assistant Professor in Urology at National Naval Medical Center at Bethesda. I am a pediatric neurologist there.

MR. SEGERSON: I am Dave Segerson, Associate Division Director, Reproductive, Abdominal, Ear, Nose, and Throat Radiological Devices. I am the FDA representative at this meeting.

DR. BENNETT: I am Alan Bennett. I am a medical consultant and Professor of Urology at Montefiore and Albert Einstein College of Medicine.

DR. VERTUNO: Leonard Vertuno. I am a nephrologist and Associate Dean at Loyola University School of Medicine, Maywood, Illinois, and I am a voting member.

MS. NEWMAN: I am Diane Newman. I am a nurse practitioner in practice in Philadelphia in incontinence, and I am the consumer representative. I am a non-voting member.

DR. DIAMOND: My name is Michael Diamond. I am Professor of Obstetrics and Gynecology at Wayne State University in Detroit, Michigan, and I am a temporary voting member.

DR. A. KALLOO: My name is Anthony Kalloo. I am Associate Professor of Medicine at Johns Hopkins University and the Clinical Director of Gastroenterology, and I am a voting member.

I will now turn the meeting over to Mary, who will

read the Executive Secretary statement.

**Executive Secretary's Statement**

MS. CORNELIUS: Good morning. Before we begin, I would like to read a statement concerning appointments to temporary voting status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, as amended April 20, 1995, Dr. Richard E. Deitrick, Michael P. Diamond, Patrick T. Hunter, and Naida B. Kalloo have been appointed as voting members by Dr. David W. Feigal, Director of the Center for Devices and Radiological Health, for this meeting of the Gastroenterology and Urology Devices Panel.

As you are aware, we have some members coming that have not arrived yet, and we can only surmise there may be some problems at the airport. Dr. Foote, thank you. You are not the only one who had trouble getting here.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The Conflict of Interest Statutes prohibits special government employees from participating in matters that could affect their or their employers' financial interests. However, the agency has determined that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the

government.

A waiver is on file for Dr. Leonard Vertuno and waivers have also been granted to Ms. Diane Newman, Drs. Michael Diamond, Craig Donatucci, and Patrick Hunter for their interest in the firms that could potentially be affected by the panel's deliberations. The waivers allow these individuals to participate fully in today's deliberations.

A limited waiver has been granted to Dr. Jenelle Foote that allows her to participate in the discussion, but not vote on the PMA before the panel today.

A copy of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-25 of the Parklawn Building.

We would also like to note for the record that the agency took into consideration certain matters regarding Ms. Newman and Drs. Diamond, Donatucci, Foote, and Hunter. These panelists reported current and past interest in firms at issue, but not in matters related to what is being discussed today. Since these matters are not related to specific issues of this meeting, the agency has determined that they may participate fully in today's deliberations.

In the event that the discussions involve other products or firms not already on the agenda for which the FDA participant has a financial interest, the participants should excuse him or herself from such involvement and the exclusion

will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Dr. Kalloo will ask all persons making statements either during the open public meeting or during the open committee discussion portions of the meeting to state their name, professional affiliation, and disclose whether they have any financial interest in any medical device company.

Finally, I would like to remind you that the remaining panel meeting scheduled for 1999 is November 18th and 19th. This meeting is only tentative. The tentative panel meetings for 2000 are January 27 and 28, April 13 and 14, August 31 and September 1, and November 30 and December 1. If the panel meeting is going to be held, I will notify panel members at least two months in advance of the meeting.

I will turn the microphone back to Dr. Kalloo.

DR. A. KALLOO: Thank you, Mary.

I would like to ask Dr. Foote to just introduce herself, her specialty.

DR. FOOTE: My name is Dr. Jenelle Foote. I am in private practice in Atlanta with clinical affiliations with Emory University and Morehouse School of Medicine. My specialty

is that of general urology with subspecialty training and expertise in neurourology and female voiding dysfunction.

DR. A. KALLOO: Thank you.

**Open Public Hearing**

We will now proceed with the Open Public Hearing section of this meeting.

I would ask at this time that all persons addressing the panel come forward to the microphone and speak clearly, as the transcriptionist is dependent on this means of providing an accurate transcription of the proceedings of the meeting.

Dr. Hawes, welcome, glad to see you. If you could just introduce yourself and your title and specialty.

DR. HAWES: My name is Rob Hawes. I am a Professor of Medicine at the Medical University of South Carolina. I am a gastroenterologist.

DR. A. KALLOO: And your voting status?

DR. HAWES: I am a voting member.

DR. A. KALLOO: Before making your presentation to the panel, please state your name and affiliation, and the nature of your financial interests in that company. Let me remind you that the definition of financial interests in the sponsor company may include: compensation for time and services of clinical investigators, their assistants and staff, in conducting the study, and in appearing at the panel meeting on behalf of the applicant; direct stake in the product under

review, that is, inventor of the product, patent holder, owner of shares of stock, et cetera; owner or part owner of the company.

Of course, no statement is necessary from employees of that company.

I would ask that all persons addressing the panel come forward to the microphone and speak clearly as the transcriptionist is dependent on this means of providing an accurate transcription of the proceedings of this meeting.

Before making your presentation to the panel, state your name and affiliation, and the nature of any financial interest you may have in the topic you are going to present.

The first speaker as listed on the agenda is Dr. Roger Dmochowski from the AUA, American Urologic Association.

**Roger R. Dmochowski, M.D.**

DR. DMOCHOWSKI: Good morning. My name is Roger Dmochowski. I am a practicing urologist in Dallas, Texas. I am here to represent the opinions of the American Urologic Association in this research. I have a clinical appointment both at the Uniformed Services University and also at the University of Texas Southwestern. I have no financial affiliations with either of the companies bringing forth their products today.

I would like to make just some general supporting statements from the American Urologic Association regarding

ongoing industry-sponsored research in incontinence.

The Executive Committee of the Board of Governors of the American Urologic Association, as well as those with specific interests in neurourology and female neurology, such as Dr. Foote and myself, feel strongly that industry-supported research is crucial for the development of new and novel techniques for the delivery of incontinence treatment for patients other than surgical techniques.

It has become obvious from our improved understanding of the pathophysiology of stress urinary incontinence in both females and males that surgery is not the only nor the best option for a significant percentage of patients. We better understand the intrinsic urethral mechanism, and there are now several methods by which we can deal with the intrinsic urethral mechanism other than pure surgical techniques.

Basically, those method involve two essential types of therapeutic delivery. One is the utilization of various injectable or bulking agents of which there are basically three categories. The three categories are biologics, either autologous or non-autologous, and synthetic materials.

The other broad option for treatment of the intrinsic urethral mechanism other than surgery is the utilization of various device-based technologies, such as intraurethral mechanisms, mechanical mechanisms, and/or injectable delivery mechanisms.

It is the opinion of the AUA that development of these mechanisms and also the injectables represents the next significant frontier in development in the treatment of stress urinary incontinence other than surgical techniques which continue to evolve.

We are very much in favor of the development of these techniques. Specifically, in the injectable market, the development of the biologics really holds great promise. We have a gold standard, which is bovine collagen, which is limited both due to durability and allergic phenomena.

We are continually seeking new and better options with more longevity and durability in terms of response and also less antigenicity and allergic reactions.

In terms of mechanism technologies that we are looking for, we are looking for small mechanical devices that can be utilized by patients without significant discomfort, with relatively broad spectrums of time delivery in terms of not having to be removed every one to two weeks, but rather can dwell for anywhere from 30 to 90 days with relative stability of response and stability of mechanical support to the patient.

So, from the standpoint of the American Urologic Association, both the injectable and device-driven technology represents a frontier for the future in the treatment of the intrinsic urethral mechanism, and we support it in its entirety from the general standpoint.

Thank you very much.

DR. A. KALLOO: Thank you.

Dr. Hunter just arrived, so while he settles down, I want to just ask him to introduce himself, his title, specialty, and his voting status. Sorry to pull you to the table so quickly, Dr. Hunter.

DR. HUNTER: Pat Hunter, Clinical Assistant Professor, University of Florida. I am also in private practice in Orlando. I have no affiliation with any of the companies or products being discussed, no financial interest. I am a voting member.

DR. A. KALLOO: Thank you.

Next, Dr. Thomas Gross will give a presentation on Postmarket Evaluation at the FDA's Center for Devices and Radiological Health.

**Dr. Thomas P. Gross**

DR. GROSS: Good morning. My name is Tom Gross. I am the Director of the Division of Postmarket Surveillance at CDRH. This morning I would like to take a few minutes of your time to talk about postmarket evaluation at CDRH.

We, in the Office of Surveillance and Biometrics, think that it is important that advisory panels are aware of postmarket programs and activities because they may directly relate to your deliberations about a product's safety and effectiveness.

[Slide.]

The objectives of this presentation are threefold: one, to describe a few of the key methods of device postmarket evaluation; present challenges in better accomplishing postmarket evaluation; and describe the pivotal role that the advisory panels can play in this arena.

[Slide.]

This slide, entitled "From Design to Obsolescence," makes three key points. One, it depicts the natural history of medical devices from design to lab/bench testing, clinical testing, FDA review, and importantly, postmarket evaluation.

Secondly, it depicts the continual feedback loops throughout the process leading to product improvements. Postmarket evaluation has an important part to play in that process, and the rest of this talk will focus on three programs within postmarket evaluation - the MDR program, postmarket surveillance under 522, and post-approval under PMA.

Thirdly, the clinical community including the advisory panel has a crucial role to play in this process of continual product improvement.

[Slide.]

As products move into the marketplace, questions of potential public health interests may arise. There may be questions about a product's long-term safety, about the performance of the device in community practice particularly as

it moves outside the confines of clinical trials.

There may be concerns about effects of change in user setting, going from professional to home use, for instance, or concerns about effects of incremental changes in technology.

There may be concerns also about adverse events or unusual patterns of adverse events.

[Slide.]

Now, let's focus on some of the programs that may address some of these questions starting with the Medical Device Reporting program or MDR.

MDR is a national surveillance system of voluntary and mandatory reports. The mandatory portion started in 1984 under the Medical Device Amendments, requiring manufacturers to report deaths and serious injuries if a medical device may have caused or contributed to the event. They were also required to report malfunctions.

Beginning in 1990, under SMDA, all user facilities, particularly nursing homes and hospitals, had to report deaths to the FDA and serious injuries to the manufacturers.

[Slide.]

All told, in the history of the MDR program, we have received slightly more than 1 million reports in our database. However, it was only in the early 1990s that we started receiving huge numbers of reports, and currently we receive about 100,000 reports per year.

These are submitted on standardized forms which capture several data elements including device specifics, event description, pertinent dates, and patient characteristics.

Reports unfortunately often have very limited information, even information on age and gender is missing from many, many reports, but they also provide critical signals to the FDA, signals that we take action on.

[Slide.]

Now, what are some of the actions prompted by the MDR program? Upon further investigation of these adverse event reports, we may be doing directed inspections of manufacturers or user facilities. It may ultimately lead to product injunctions or seizures, product recall, namely, an example of a recent recall involving blood tubing associated with leaking of infected blood into dialysis machines.

We have had several patient and physician notifications over the past few years, again, many related to dialysis machines and, in particular, dialyzer membranes. Actions may also lead to additional postmarket study.

[Slide.]

We at CDRH have two authorities by which we can conduct postmarket studies. One is a statutory authority under FDAMA, Section 522, entitled "Postmarket Surveillance." Another is our post-approval authority under PMA regulation.

Section 522 was originally mandated in SMDA 1990, and

was changed significantly in FDAMA 1997. The 1990 version had categories and lists of devices, the manufacturers of which were required to do postmarket studies on regardless of whether there were any pertinent public health questions.

Those categories and lists were deleted and they are no longer part of the FDAMA 1997 version. However, the '97 version retained FDA's discretionary authority to order postmarket surveillance on products for which we had public health concerns.

Now, post-approval refers to PMA products and it is reserved strictly for PMA products and the studies conducted under post-approval are referred to as conditions of approval studies. Section 522 extends our authority to cover Class II and III 510(k) products whose failure may present a public health problem.

Now, both authorities are seen as a complement to the premarket efforts to continually assure product safety and effectiveness in the marketplace.

[Slide.]

Now, in implementing the FDAMA version of Section 522, we developed criteria to help guide our deliberations about when to impose postmarket surveillance on Class II and III products. The principal criterion is that there has to be a critical public health question.

This can result from a "for cause" issue, such as a

notable adverse event or patterns of adverse event. It may be linked to concerns about new or expanded conditions of use, or concerns about safety related to the evolution of the technology.

The second criterion has to do with consideration of other postmarket strategies, 522 may not be the appropriate strategy to answer the public health question of interest - perhaps an inspection, perhaps some aspect of the quality systems regulation would better handle the issue.

Thirdly, the studies have to be practical and feasible to conduct. For instance, for long-term studies we need to be somewhat assured that sufficient patient follow up is there.

A related question - how will the data be used? This is especially important for rapidly evolving technology. By the time the studies are done, the data may be obsolete.

Lastly, it has to be of a high priority for the center, for yourselves, and for the manufacturing community.

[Slide.]

Once we decide to impose postmarket surveillance under 522, there are several approaches we may use. We should attempt to choose the appropriate study design to match the public health question of interest and to choose the least burdensome approach.

Now, that may mean something as least burdensome as a

detailed review of the complaint history and literature, non-clinical testing of a device, use of existing databases, or telephone or mail follow up of patients. It may require something more sophisticated, such as use of product registries, case control studies, and rarely, we might turn to randomized trials.

[Slide.]

Now, what are some of the frustrations we have experienced in conducting postmarket surveillance in the postmarket period?

I have mentioned before that the rapid evolution of technology may make studies obsolete. We should anticipate that. There are lack of incentives for industry to conduct these studies. Industry may view these studies as being the bearers of only bad news for their products. We need to change the paradigm and make it useful for industry to conduct these studies.

There may be lack of interest in the clinical community. Clinicians may be much more interested in studying cutting-edge technology as opposed to issues related to mature technologies.

As in the case of SMDA 1990, there may be lack of clearly specified public health questions.

[Slide.]

Now, what is the challenge to the advisory panel and

really the challenge to us all?

When considering postmarket studies, whether they are post-approval or 522, we need to ensure that these are of primary importance, that they are just not nice to know, that they are central to the issue of the safety and effectiveness of the product, that they justify the resources, that they are practical and feasible.

We need to clearly specify the public health question, and we need to note the clinical and regulatory relevance of answering the question - what will do with the data? Are the data there to assure us that what we see in the postmarket arena is what we have seen premarket, are they there to address residual concerns about the product, are they there to capture untoward events?

[Slide.]

Lastly, this is my last slide, just a look into the future of MDR and postmarket surveillance.

For medical device reporting, we are moving more and more away in terms of efficiency from individual reporting to summary reporting of well known and well characterized events, and we are also looking into a sentinel reporting system. Rather than having the universe of hospitals report to us, we are working on establishing a subset of hospitals who are well trained, well informed about recognizing medical device issues, so that we can obtain much more timely and higher quality

reports.

We are also working on submission of reports electronically. Today, we get them hard copy. We are looking to integrate trend analyses with the quality system regulations, and we are also in the process of exchanging reports internationally and globally.

Under postmarket surveillance, I have mentioned there are a wider variety of design approaches that we should choose from. There should be more collaboration with industry and the clinical community, and there should be expanded access to relevant data sources.

That finishes my brief talk, and I will take any questions if there are any.

DR. A. KALLOO: Any questions?

DR. DONATUCCI: I just have one question. How many devices have actually been recalled under the postmarket registry program? In other words, how many times --

DR. GROSS: Have we instituted postmarket surveillance?

DR. DONATUCCI: No, that you have instituted, but that has resulted in the disapproval or revocation of approval of a device.

DR. GROSS: I think it's fair to say never. I am not sure about the PMA side of the house, but I don't think it has ever resulted in a product withdrawal, and somebody on the OD

side can correct me if I am wrong.

With regard to the Section 522 authority, that is a relatively new program, and it underwent significant changes last year, so we have a very brief history, and it has not resulted in any product withdrawals.

The purpose, if I didn't make it clear, is not really to recall a product. The purpose is to set up studies to address either "for cause" issues or potential issues about the safety of a product.

DR. DONATUCCI: Right, but the public health question ultimately is that a device was approved and placed into use before an unanticipated problem arose. I mean I am thinking of an analogous situation to drugs, such as the anti-obesity drugs that were then pulled because of the possible cardiac toxicity.

So, as of today, there is no analogous situation, no device has actually be subject to that?

DR. GROSS: Not under those authorities. We recall products under different mechanisms, but not under those authorities, but let me give you a more concrete example. Polyurethane foam-coated breast implants. They were marketed a few years back, and some years into its marketing, there were questions raised about its possible carcinogenicity based on animal studies.

We ordered the company to do a study to help resolve that issue, and they did a small-scale study involving humans,

blood testing and urine testing, and the upshot of that study was that there was no significant risk of carcinogenicity based on those data.

So, in that instance, it helped reassure us that at least for that particular issue and for that particular product, there was no long a major public health concern. So, that is one concrete example. Of course, it didn't result in any product withdrawal.

DR. DONATUCCI: I guess the thrust behind my question is that regardless of whether it's PMA 522 or other mechanism, the process that you have in place now for device approval has served the public well. There hasn't been major problems that have not been identified through this process. Am I correct in that assumption?

DR. GROSS: Well, I think it has served us well, and you still have the authority to conduct these condition of approval studies. There are several other mechanisms by which we monitor products. I alluded to one, the Medical Device Reporting mechanism where we received adverse event reports, and there are multiple things that we can do based on those adverse event reports.

One of them -- maybe I should bring the slide back up -- is ordering additional postmarket studies. The other things we can do is we could directly inspect a firm, we can ultimately seize the product, we can ultimately recall the product, and

this is absent any postmarket study.

DR. DONATUCCI: Those are what you can do. My question actually was how often have you actually done that.

DR. GROSS: Well, absent a postmarket study, we conduct recalls at least -- I am talking about the entire agency -- I know for a fact several thousand a year. This is absente postmarket studies. This is using other mechanisms by which we surveil products.

The agency, as a whole, including drugs and biologics and devices, conduct several thousand recalls a year.

DR. DONATUCCI: I guess the thrust of my question again is devices and how often does that happen.

DR. GROSS: Devices, I wish I had the exact numbers, but I believe several hundred. I can clarify that if anybody else has more current information, but it is a substantial number.

DR. A. KALLOO: Any other questions?

DR. HUNTER: I have one. Having been a panel member for a number of years, I have helped recommend postmarket approval studies, and I am wondering what your routine is to help check on those, and then I think some of them are commerce. I am now looking back, and the marketplace is very shrewd at finding a device that although it's not dangerous, is no longer effective, and if you have a system in place to say, hey, enough, or have a review and say enough, we can stop these

studies, or do you have a routine way of doing that, because it would be cumbersome on the agency to continue every study that we recommend.

DR. GROSS: Well, there is a mechanism, at least on the PMA side, where they get annual reports, and they are required to look at the information submitted on these interim reports, and basically follow through to make sure that those studies are complete.

We are starting a process right now on reviewing how well that process works. Now, on the 522 side of the house, a related authority, as you can gather, we have changed the program significantly because of the statutory changes. I mentioned the 1990 and 1997 version.

So, we have a limited history with the new approach, but our intent is, as you say, is to monitor these studies to see if they are being conducted, to see how useful they are ultimately, and to change our approach if that doesn't work.

DR. BENNETT: Following up on Craig's issues, and being the industry rep, I understand that the annual reports are done, however, I would encourage you and the agency to really fine-tune that as rapidly as possible.

I have rather direct experience in a very prolonged postmarket study that will never, ever be able to be completed on a product that has been on the market for almost a decade, and going back to the issue that Craig brought up, there are

other mechanisms, and I would behoove the FDA to try to step in and when you find and realize that a postmarket approval study really is not adding anything, then, be proactive rather than wait for the study to be completed.

DR. GROSS: I would second that. You should be aware of reengineering efforts that have been going on within the center, and there is one initiated recently on postmarket reengineering, and that is one of the topics for the reengineering.

DR. BENNETT: If you need a specific example, I will be more than happy to give it to you.

DR. GROSS: I am sure you would and I would appreciate that.

DR. A. KALLOO: Thank you, Dr. Gross.

Next, Don St. Pierre will bring us up to date on the progress made on matters previously presented before the panel.

Don.

**Donald St. Pierre**

MR. ST. PIERRE: Good morning. I am Donald St. Pierre, the Branch Chief of the Urology and Lithotripsy Devices Branch. As is customary, I will give a brief update regarding our past panel meetings, which is not terribly customary, I am going to actually follow a script this time.

Our last meeting was held on October 29, 1998. At this meeting the panel made a recommendation of approval with

conditions on a PMA Supplement from Cypress Bioscience, Inc., for an extracorporeal immunoadsorption device called the Prosorba column indicated for use in the therapeutic reduction of the signs and symptoms of moderate to severe rheumatoid arthritis in adult patients with long-standing disease who have failed or are intolerant to disease-modifying anti-rheumatic drugs. FDA agreed with the panel's recommendation and issued an approval order on March 15, 1999.

I would now like to update you on some other activities that were subject to earlier panel meetings. First, on July 30, 1998, the panel made a recommendation to down-classify extracorporeal shock wave lithotripters from Class III to Class II and also provided recommendations on a special controls guidance document for extracorporeal shock wave lithotripters.

This was an FDA-initiated down-classification. FDA agreed with the panel's recommendations and issued a proposed rule on February 8, 1999, to down-classify these devices. On the same date, FDA also issued a Level 1 draft guidance document in accordance with our internal good guidance practices. The comment period on these documents ended on May 10. We are in the process of addressing the comments and preparing the final rule and final guidance document.

Going back a little further, on February 12, 1998, a closed panel meeting was held to discuss a product development

protocol, commonly referred to as a PDP, for American Medical Systems' penile inflatable implants.

I am pleased to announce that the company completed their PDP and was given marketing approval on November 2, 1998. This represents the first ever completed PDP for the agency and will ensure the continued availability of these types of products when the final rule is published calling for PMAs or PDPs.

For those of that are unfamiliar with the PDP process, it is an approval process that has always been in the regulation, but has never been used successfully until now. As part of CDRH's reengineering efforts, this process was given new life. For more information on the PDP process, I suggest that you check out CDRH's web site.

The next couple of notable device approvals that I will discuss involve implantable stimulators. Although not subject to a previous panel meeting, I mention these because the agency used guidance that was provided by the panel in a previous panel meeting.

This panel met on August 6, 1997, to provide recommendations on Medtronic's Implantable Sacral Nerve Stimulator for the treatment of urinary urge incontinence in patients that failed or could not tolerate more conservative treatments.

Based on the panel recommendations, FDA approved this

device on September 29, 1997. Subsequent to that approval, Medtronic submitted a PMA supplement to expand the indications to include urinary retention and treatment of patients with significant symptoms of urgency/frequency.

The agency determined that based on the panel's deliberations at the August 6, 1997, panel meeting on the original PMA application provided sufficient guidance and we did not bring this before another panel. The device with the expanded indications was approved on April 15, 1999.

The agency has also approved two humanitarian device exemptions for an implantable stimulator. Like the PDP, the HDE is another fairly new program which is directed at devices that treat conditions affecting less than 4,000 patients a year.

This is CDRH's equivalent to orphan drugs. An HDE requires that the sponsor demonstrate that their device is safe and has probable benefit.

FDA used the knowledge gained from the August 6, 1997, panel meeting and applied it to the review of NeuroControl Corporation's VOCARE Bladder system which is indicated for the treatment of patients who have clinically complete spinal cord lesions with intact parasympathetic innervation of the bladder and are skeletally mature and neurologically stable, to provide urination on demand and to reduce post-void residual volumes of urine.

The VOCARE system was approved on December 28, 1998.

NeuroControl Corporation submitted another HDE to add a secondary indication to aid in bowel evacuation. This secondary use was approved on February 19, 1999.

I would now like to follow up on a couple of issues that Dr. Gross just discussed regarding two specific post-approval studies that have been completed in urology.

As you may know, in December of 1988, the panel recommended that all original PMA approvals for extracorporeal shock wave lithotripters have as a condition of approval, a requirement that a post-approval study be conducted to study the relationship between lithotripsy and hypertension.

The condition of this post-approval study requirement has resulted in a labeling change for extracorporeal shock wave lithotripters that changed the statement that the risk of hypertension is unknown to the statement that hypertension is not a long term risk of lithotripsy.

This was further emphasized at last year's panel meeting on the down-classification of extracorporeal shock wave lithotripsy.

The second successful completion of a post-approval study involves a device for the treatment of BPH. On May 3, 1996, FDA approved EDAP Technomed's PMA for the Prostatron which is a microwave thermal therapy system for treating BPH.

This device was discussed at a panel meeting on October 20, 1995, and the panel recommended approval with

conditions. One of the conditions was the completion of a post-approval study to assess the long-term effects, that is, five year years posttreatment, including durability and re-treatment rates.

The sponsor completed the study and modified their labeling to include five-year follow-up data. Both of these studies demonstrate the benefits of a well-thought-out post-approval study.

This concludes my update on past panel activities.

Thank you.

DR. A. KALLOO: Thank you. Any questions for Don?

If there is anyone else wishing to address the panel, please raise your hand and you may have an opportunity to speak.

[No response.]

DR. A. KALLOO: Since there are no other requests noted, we will now proceed to the open committee discussion of the premarket approval for P980053 Advanced UroScience Durasphere (urethral bulking agent) as indicated for the treatment of stress urinary incontinence due to intrinsic sphincter insufficiency. This device is injected into the urethral submucosa under endoscopic vision to achieve urethral bulking and coaptation.

I would like to remind public observers at this meeting that while this portion of the meeting is open to public observation, public attendees may not participate except at the

specific request of the panel.

The first speaker for the sponsor is Karen Peterson.

I was just told that we have more panel members, Dr. Deitrick and Dr. Steinbach. If you could please introduce yourself, your specialty, and your voting status, please.

DR. STEINBACH: My name is Joseph Steinbach. I am at the University of California at San Diego. I am an engineer/biostatistician, and my voting status, I am a panel member, I vote.

DR. DEITRICK: I am Richard Deitrick, Chairman of the Department of Ob-Gyn at Mercy Hospital in Pittsburgh.

DR. A. KALLOO: And your voting status?

DR. DEITRICK: Panel member, yes.

DR. A. KALLOO: The first speaker for the sponsor is Karen Peterson.

I would like to remind the speakers please disclose whether they have financial interests in any medical device company and, if so, please state your financial interest.

**PMA P980053**

**Advanced UroScience Durasphere**

**(Urethral Bulking Agent)**

**Sponsor Presentation**

**Introductory Remarks and Product Description**

**Karen Peterson, M.S.**

MS. PETERSON: Good morning, Mr. Chairman and

distinguished panel members. My name is Karen Peterson and I am the Vice President of Regulatory, Clinical and Quality Affairs for Advanced UroScience.

[Slide.]

I would like to begin by introducing the other individuals in attendance today who are representing Advanced UroScience. Dr. Jeffrey Snyder, urologist from Denver, Colorado, who is one of the investigators in the clinical trial. Dr. Aaron Kirkemo, consulting urologist from St. Paul, Minnesota. Attending from Advanced UroScience today is Dean Klein, our President and CEO; Richard Holcomb, our biostatistician, and Tina Wittchow, our Clinical Research Manager.

[Slide.]

We are very pleased today to present our marketing application for Durasphere Injectable Bulking Agent for the treatment of stress urinary incontinence due to intrinsic sphincteric deficiency, or ISD.

[Slide.]

Our presentation today will be conducted in four parts. I will summarize the prevalence of urinary incontinence, and I will provide you with the product description. Richard Holcomb will present an overview of the clinical trial study design and the protocol.

Dr. Jeffrey Snyder will summarize the injection

procedure and present the safety and effectiveness results from the clinical trial. Then, I will present some concluding remarks.

[Slide.]

Urinary incontinence is a common condition. According to the U.S. Department of Health and Human Services, urinary incontinence plagues 11 to 35 percent of adults and at least half of the 1.5 million nursing home residents in the United States.

At least 13 million American adults suffer from some form of urinary incontinence, and 85 percent of them are women. Urinary incontinence is generally recognized as one of the major causes of institutionalization in the elderly.

[Slide.]

Stress urinary incontinence due to ISD is a condition where the bladder neck does not close properly. Involuntary loss of urine occurs during a stress event such as coughing, sneezing, laughing or other physical activities that increase the abdominal pressure.

Durasphere is injected trans-urethrally under direct visualization, through a cystoscope or endoscope into the mucosal lining of the bladder neck or urethra. Durasphere is injected using a commercially available injection needle. Durasphere is designed to create increased tissue bulk and subsequent coaptation of the bladder neck or urethra to prevent

involuntary loss of urine. Here you can see the demonstration of the increased tissue bulk.

[Slide.]

Durasphere is a sterile, injectable bulking agent composed of pyrolytic carbon-coated beads suspended in a water-based beta-glucan carrier gel. Durasphere is dispensed in a commercially available, individually packaged one-milliliter syringe.

[Slide.]

The size range of the beads is 212 to 500 microns, which has been deliberately chosen to be well above any known threshold for migration. Published studies in the urology literature have reported that migration has been associated with particles less than 80 microns in size.

The carrier gel consists of 2.8 percent beta- glucan in water. Beta-glucan is a simple polysaccharide and has a well-established role as a nutrition supplement and as an agent to facilitate wound healing. The combination of water and beta-glucan in this ratio produces a viscous, biocompatible carrier gel suitable for suspending the pyrolytic carbon-coated beads.

[Slide.]

Injectable bulking agents and injection techniques for the treatment of stress urinary incontinence due to ISD are not new. Contigen, manufactured by Collagen Corporation and

distributed by C.R. Bard, was introduced for use in the United States in 1993. Contigen is currently the only injectable bulking agent available in the U.S. for the treatment of stress urinary incontinence due to ISD.

Durasphere was specifically designed to be biocompatible, non-immunogenic, non-migratory, and non-absorbable.

[Slide.]

I would now like to introduce Richard Holcomb, who is going to provide you with an overview of the study design and the protocol.

**Study Design and Protocol**

**Richard Holcomb, Ph.D.**

DR. HOLCOMB: Good morning. My name is Richard Holcomb. I am a biostatistician for Advanced UroScience, and I am pleased to present highlights of the study design for the Durasphere clinical study.

[Slide.]

The goal of this IDE study was to evaluate the safety, effectiveness, and performance of the Durasphere for the treatment of stress urinary incontinence due to ISD in male and female adults.

The specific objectives of the study include:

1. Evaluating the effectiveness of Durasphere in improving the patient's incontinence over a one-year period

commencing with their first treatment.

2. Assessing the safety of Durasphere by quantifying any adverse health effects during and after the transurethral injectable procedure.

3. Comparing the safety and effectiveness of Durasphere for the treatment of stress urinary incontinence with the safety and effectiveness of the control.

[Slide.]

This study was designed as a multi-center, double-blinded, randomized, controlled trial. Patients were assigned to receive either the Durasphere or the market-released control product, Contigen.

The randomization was one-to-one between Durasphere and control and was stratified by the gender of the subjects and blocked within clinical sites to achieve a balance between study centers.

The study was a double-blind trial. Due to the nature and treatment and anatomy involved, patients would be blinded to the treatment they received. Treating physicians could not be blinded, however, due to the differences in the study material, because of the different appearance and handling characteristics, as well as packaging. However, study staff and non-treating physicians who performed the follow-up evaluations were blinded to the therapy.

[Slide.]

The study had two primary efficacy endpoints.

The first endpoint was the change in the continence grade score of the patient from baseline to the 12-month posttreatment interval time point. This endpoint was used to determine the required sample size. A decrease in the continence grade of one or more grades was considered a success for purposes of evaluating this endpoint.

[Slide.]

The continence grades used for the study and involved in the success criteria were defined by Stamey in 1979 and have been used frequently in incontinence studies including the prior Contigen clinical trial.

This is a four-point scale from zero to 3, with zero indicating a continent or dry status of the patient; Grade 1, some loss of urine with increases in abdominal pressure; Grade 2, a worsening of incontinence associated with physical activities; and Grade 3, associated with total incontinence and urine lost without any relation to activity or position.

[Slide.]

The second primary efficacy endpoint for the study was based on urine loss during pad weighing testing, and also evaluated the improvement from baseline to 12 months post-treatment.

[Slide.]

This pad weight endpoint was measured by evaluating

the urine loss of patients who underwent a prescribed set of activities included in the protocol that led to stress incontinence. This urine loss was quantified through the use of pads, which were worn by the patients and then weighed at the completion of the activities.

[Slide.]

The primary endpoint of safety was evaluated through an analysis of morbidity and complication rates associated with the use of Durasphere, and the evaluation of those risks.

Safety was assessed by the physician through physical examinations and by questioning patients immediately post-injection and at all subsequent follow-ups.

Symptoms and complications were recorded for all patients. The investigators were instructed to report any symptom or adverse event, and to rate each experience for the intensity, duration, possible cause, and eventual outcome of that adverse event. All reports of adverse experiences were reviewed and classified additionally by the nature and severity of the event, as well as the relationship of the event to the device or the treatment procedure.

[Slide.]

Investigators classified these adverse events as mild, moderate, or severe: mild events being defined as those requiring minimal medical treatment; moderate events being associated with temporary disability or other medical or

surgical interventions; and severe events defined as one that were associated with life-threatening episodes.

[Slide.]

A number of secondary endpoints were also evaluated statistically in the study. These included the following:

1. The number of patients who had improved in continence grade at follow-ups before and after one year.

2. The number of patients who were dry, that is, an incontinence grade of zero at each follow-up interval.

3. The total number of treatments required including re-treatments.

4. The volumes of the Durasphere and control materials injected.

5. Changes in an incontinence-specific validated quality of life instrument.

[Slide.]

Initial sample sizes were calculated for evaluation of the primary study endpoint of incontinence grade change based on the Blackwelder approach through equivalence trials, with a design criteria of a Type 1 error alpha of 0.05 and an 80 percent statistical power. This led to an estimate of 232 patients to be followed for one year.

[Slide.]

Summary statistics were calculated for all study variables. These included the common summary measures of

mean,s, standard deviations, standard errors, and the like.

Differences in continuous variables between the treatment groups or between phases of the study were evaluated using two-sample tests, such as Student's t-tests. Within-patient differences were evaluated using paired tests, and where there was evidence of non-normality of any of the responses, appropriate nonparametric tests were used or evaluated including Wilcoxin and Mann-Whitney tests.

Evaluations of more than two independent groups, such as evaluation of clinic differences, employed analyses of variances or their nonparametric equivalent. Comparisons of categorical variables employed Fisher's Exact Tests, thereby not depending on the distribution of the responses, and in either the report or subsequent communications with the FDA, multiple analyses, multiple regression analyses, and other multivariable analyses were performed including logistic regressions and repeated measures analyses.

Unless otherwise indicated, all statistical tests were two-sided, with p-values of less than 0.05 or equal to 0.05 considered evidence of statistical significance.

[Slide.]

Upon enrollment into the study, baseline patient and medical history data relevant to the diagnosis of stress urinary incontinence were collected. At baseline and follow-up visits, data were also collected on the results of laboratory blood and

urine testing, abdominal leak point pressure testing, pad weight tests, seven-day voiding diaries, and Quality of Life instruments.

In addition to the assessment of changes in continence grade at scheduled follow-up visits, data were recorded on any procedure- or urology-related symptoms, side effects, and safety issues seen by the physician or reported by the patient.

A maximum of four re-treatments was allowed in the study, consistent with the labeling for the control device. Re-treatment was to occur when the patient had not improved or when the investigator believed that another treatment would be beneficial to the patient.

[Slide.]

At this point, I would like to introduce Dr. Jeffrey Snyder from Denver Colorado, who will summarize the injection procedure and the clinical study results.

Thank you.

**Injection Procedure and Clinical Study Results**

**Jeffrey Snyder, M.D.**

DR. SNYDER: Good morning, Mr. Chairman and panel members. I am very pleased to have this opportunity to advance what I believe is a safe and effective treatment for stress urinary incontinence due to intrinsic sphincter deficiency. The urology community anxiously awaits an a non-immunogenic urethral

bulking agent.

First, let me disclose that I have no financial ties with Advanced UroScience other than that as a clinical investigator and as a consultant.

[Slide.]

I am going to begin my presentation today by showing you a video of an actual injectable procedure that was performed from one of our sites that occurred during the clinical trial, to demonstrate the simplicity of this injectable technique.

This is an example of a cystoscopic view looking into the bladder. At the 5 o'clock position, we see the injection needle. This is quite an intuitive procedure for any urologist or gynecologist who performs cystoscopic procedures. We have an open bladder neck. The needle is advanced into the submucosal region. The needle has been primed with the Durasphere, and you can see, with infiltration and implantation, you get bulking of this area in the submucosal region, a bulk mass effect, and you see closure of the bladder neck region.

This is quite a simple procedure with a very short learning curve, and this is quite easily accomplished and was demonstrated by all our sites, and you can see closure of the bladder neck.

It is very interesting to look at the device. As you can see, although there is a puncture site here with the implants, it does not, because of the impregnation in the

beta-glucan gel, does not leak out of this area, and it is surmised and believed that this will be something that is important for the long-term durability of this very biocompatible and non-immunogenic implant.

A second puncture site is created at the 7 o'clock position. The sites of puncture are very operator-dependent and what we are looking for is just coaptation and decrease of this lumen in the bladder neck.

One starts very proximally in the urethra and works more distally. This is an analogous situation in the male patient, as well, and this is obviously a female patient.

[Slide.]

In summary, this minimally invasive, simply injection procedure takes less than a half-hour and is easily accomplished in an outpatient setting. For physicians experienced with injectable bulking agents, this procedure is routine and quite intuitive to begin.

[Slide.]

In June 1996, Advanced UroScience began this investigational study of Durasphere injectable bulking agent. A total of 377 patients were injected with either the Durasphere or the control bulking agent at 10 investigational centers. The data includes all patients treated in the study as of December 1, 1998, and all follow-up data received up until May 21, 1999.

This IDE study was open to both men and women. Of

these 377 patients, 355 patients were female and 22 were male. Based upon anatomical and etiologic differences in their incontinence, it was expected that the treatment outcomes would be gender specific. Thus, study results were reported separately for men and for women.

The male patients experienced less improvement than the female counterparts. However, these improvements, as well as the overall clinical results, were similar in male patients between Durasphere and the control.

I will now be presenting the results from the female population in the study.

The Durasphere female population were followed in the study for a mean of 10.7 months with a cumulative study time of 1,997 months. As required, at least 232 female patients were evaluated at one year post-injection.

[Slide.]

This busy slide displays the baseline characteristics of the patients receiving Durasphere and the control product. There was no significant difference between the Durasphere and the control patients for any of the baseline variables. This was a very well matched group of patients.

[Slide.]

The first primary endpoint is the percentage of patients improved by greater than or equal to 1 continence grade based upon the Stamey system at 12 months. As shown in the

slide, 66.1 percent of Durasphere patients and 65.8 percent of the control patients demonstrated an improvement in the continence grade of greater than or equal to 1 at 12 months. No significant difference was observed between Durasphere and the control group.

This primary endpoint was also evaluated using the Blackwelder method, in which the Durasphere device was found to be equivalent to that of the control, with a p-value of 0.007.

[Slide.]

The second primary endpoint is the change in pad weight from baseline to 12 months. As shown in the slide, the mean change or decrease in weight in pad weight from baseline to 12 months was 27.9 grams in the Durasphere group and 26.4 grams in the control group. No significant difference was observed between Durasphere and the control.

In summary, what we can say is there is no significant difference in the two primary efficacy endpoints between Durasphere and the control group. It is therefore concluded that the effectiveness objective of the study has been met and that Durasphere's effectiveness is equivalent to that of the commercially available control group.

[Slide.]

I would now like to present the results of the safety data of the primary safety endpoints, namely adverse events experienced during the clinical trial. It is important to point

out that Advanced UroScience included all symptoms and observations reported on the case report forms regardless of whether or not they were related to the study product. Many of the events were unrelated to the study, but were included by the sponsor for completeness.

This slide demonstrates all of the mild, moderate, and severe adverse events by severity distribution. The mild category consisted of 87.6 percent of Durasphere events, 11.6 percent as moderate, and 0.8 percent of severe events.

The three events considered severe for the Durasphere patient included patients with chest pain, renal failure, and myocardial infarction. All three events were deemed unrelated to the device or to the procedure by the clinical investigators.

There was no significant difference seen in the distribution of severity of events between Durasphere patients and the control group.

[Slide.]

This slide shows the incidence of the adverse events that were reported by 10 percent or more of the Durasphere patients.

There were a total of 31 different categories of adverse events reported during the study. Once again, there was no significant difference in the incidence of events between the Durasphere and the control group for 29 of the 31 groups.

However, there was a significantly higher incidence

of urgency and acute urinary retention, defined for duration less than seven days, for Durasphere for the control patients, with the p-values of 0.002 and less than 0.001, respectively, and I will address these two different categories in my next two slides.

[Slide.]

With regard to urinary retention, 30 Durasphere patients experiences symptoms of acute urinary retention, defined as inability to void or the sensation of incomplete bladder emptying, following treatment.

Twenty cases were resolved after short-term catheterization, and one case the treating physician chose to remove 2 ml of material by aspiration in a transvaginal fashion, thereby allowing the patient to void. Nine cases resolved on their own without any intervention.

All cases of acute urinary retention were resolved on an average of four days with a maximum of seven days post-treatment. No untoward consequences were experienced by any of these patients, nor was there any adverse impact on continence improvement.

[Slide.]

With regard to the urgency issue, 44 Durasphere patients experienced urgency some time in the study. Thirteen of these patients reported symptoms of urgency prior to entering the study, therefore, we are discussing 31 patients who

experienced de novo or new onset of urgency.

The vast majority of these urgency symptoms that were reported were resolved and required limited medical intervention. Eighteen cases resolved on their own without any intervention, and 12 of the remaining 13 were resolved with medication.

All urgency events treated with medications were considered mild. Twelve of the 13 events resolved on an average within 57 days. One patient remains on Ditropan, a bladder antispasmodic, for the treatment on urgency at the time the database was closed in May.

It is certainly worth noting that the proportion of Durasphere urgency events that were resolved were significantly better than that of the control group. As of the time of the database closure, 90 percent of the urgency events for Durasphere were completely resolved as compared to 65 percent of the urgency events for the control group. The p-value for this difference was 0.021.

[Slide.]

The mean duration and resolution of all adverse events are displayed on the slide.

The duration of an adverse event was calculated by subtracting the onset date from the date that the event was documented to be resolved. As shown in this slide, the overall mean duration of all adverse events was significantly lower or

better clinically for Durasphere compared to the control group, with a p-value of 0.032.

Overall, 91 percent of the Durasphere events were resolved as of the database closure as compared to 87 percent of the control group events.

[Slide.]

Our adverse event summary. This slide demonstrates the overall adverse event profile of Durasphere patients and the control group patients is actually quite similar. This is based on the evaluation of the four adverse events attributed as just discussed - the severity, the incidence, duration of the events, and resolution of the events.

There was no difference between groups in the severity of the events. If you multiply the number of events by the duration of events you obtain total adverse event days. Although the number of events was higher for Durasphere, the duration was longer for the control group. Therefore, the combined total adverse event days was similar between the two groups.

Finally, there was no difference between groups in the resolution of these events. We conclude, therefore, that the overall adverse event profile is similar between Durasphere and the control group.

[Slide.]

Looking at our secondary endpoints now, in the next

few slides I will summarize the secondary endpoint results of the study. This slide demonstrates and displays the improvement in continence grade at the various follow-up periods of one month, three months, six months, 12 months, and 18 months for the Durasphere patients.

As can be easily seen by this bar graph, the mean continence grade was significantly and consistently improved from baseline to follow-up, all the way across all the time periods for the Durasphere patients. The p-value was 0.001.

Interestingly, at the 12-month period, the mean continence rate for Durasphere was significantly improved from 1.8 at baseline to 0.97. This represents a 48 percent improvement in the mean continence grade.

No significant difference in mean change of continence grade was observed between Durasphere and the control group at any of the follow-up visits.

Secondary endpoints improvement of greater or equal to one continence grade.

[Slide.]

This table displays the proportion of Durasphere and control group patients who have improved by one or more continence grades from baseline to the time of their follow-ups. No significant difference was observed between the proportion of Durasphere and control group patients who demonstrated improvement by greater than or equal to one continence grade at

anytime in the follow-ups. These are very equivalent groups at all follow-up areas up to 18 months.

Previous studies on the control population reported the proportion of patients demonstrating improvement at some time during the study. For comparative purposes, 90 percent of Durasphere patients and 89 percent of the control patients demonstrated an improvement of equal to or greater than one continence grade at some time during the study.

[Slide.]

There was no significant difference in the proportion of patients who achieved a continence grade of zero, defined as dry, between the patients in the two groups at any time in the follow-up visits.

[Slide.]

This slide depicts pad weight test by time. This next figure displays the improvement in pad weight of the Durasphere population in the time periods, and what we can observe is a decrease in pad weight test at all parameters of one month through 18 months.

The mean pad weight was significantly improved or reduced from baseline to follow-up at all time periods for Durasphere patients, with a p-value of less than 0.001. These results parallel the graph recently shown for improvement for continence grade.

The mean pad weight for Durasphere patients was

significantly improved from 47.2 grams at baseline to 19.3 grams at the 12-month period. This also represents a 59 percent reduction in pad weight at 12 months.

No significant difference in pad weight was determined between the Durasphere group and the control group.

[Slide.]

Patients were required to complete a voiding diary once week prior to each follow-up visit. This figure displays the improvement in incontinence episodes per week by time periods for the Durasphere population.

The mean number of episodes per week was significantly improved from baseline to follow-up at one, three, six, and 12 months for the Durasphere patients, with a p-value of 0.001.

I want to bring your attention to the improvement at all these time parameters and the similarity in the parameters they were measuring in the secondary endpoints. There is quite a bit of consistency in this product.

At 12 months, the mean number of episodes per week was significantly improved from 20.8 episodes per week to 10.2 episodes per week at 12 months. This represents an improvement of 51 percent.

No significant difference in change in number of incontinence episodes from baseline to follow-up was observed during this trial between Durasphere and the control group.

[Slide.]

This slide depicts Quality of Life and the Quality of Life survey scores that were determined during the time periods of the Durasphere study population. The mean incontinence Quality of Life score was significantly improved from baseline to follow-up at all time periods for the Durasphere patients. The p-value was less than 0.001.

At 12 months post-treatment, the mean score of Durasphere patients was significantly improved from 55.5 at baseline to 73.7 at the 12-month period. This represents an improvement of symptoms of 33 percent in the incontinence Quality of Life score at 12 months.

No significant difference in the mean change of incontinence Quality of Life scores from baseline to follow-up was observed between the two groups at any of the follow-ups.

[Slide.]

Number of injections. The distribution of the total number of treatments that each patient received during the study is displayed on this graph. The mean number of Durasphere injections per patient during the clinical trial was 1.69. There was no significant difference in the number of treatments between the Durasphere patients and the control patients.

[Slide.]

Injection volume. This table represents the mean volume of material injected at the initial treatment for

Durasphere and control patients, as well as the total volume of material injected for patients during the study.

The Durasphere patients had a mean of 4.8 ml of material injected at the initial injection as compared to the control group of 6.2 ml. The total mean volume of material injected during the study was, on average, 7.6 ml for the Durasphere patients and 9.6 ml for the control patients. Thus, Durasphere patients had significantly less material injected at the initial injection time, as well as total injection material, less was injected during the study. The p-value of this was 0.001. Whether this difference is clinically significant still remains to be determined.

[Slide.]

Durability. One of the potential advantages of Durasphere over the control group material is the fact that Durasphere beads are non-absorbable, whereas, collagen is absorbed by the body over time. In theory, one would expect the Durasphere implants to be more durable.

My final two slides give some insight into the durability of Durasphere compared to the control.

The fact that the re-treatments were allowed to occur throughout the study confounds the results of the durability tests. If one were to evaluate the patients who received a single injection during the study, it would show how these patients endured over time without additional treatments.

This slide shows the improvement in continence grade by follow-up for all patients who received a single injection during the study for both Durasphere and control. At one year post-treatment, 83.7 percent of Durasphere patients as compared to 71.4 percent of control patients were improved by greater than or equal to one continence grade compared to baseline. Remember that these are patients who received only one single treatment. The p-value for this difference is 0.166, which is suggestive but clearly not significantly different.

[Slide.]

My final slide shows the results as if were to analyze the data in a slightly different way, or the retrospective way, that is looking at improvement one year after the last injection was received and looking back.

This table demonstrates that 80.3 percent of the Durasphere patients and only 69.1 percent of the control group patients were improved by one continence grade one year after their last injection. The p-value of this difference is 0.162, which is again suggestive but clearly not significantly different.

[Slide.]

This concludes my presentation of the clinical studies. Thank you for the opportunity. I will now call upon Karen Peterson to provide you with her concluding remarks.

DR. A. KALLOO: Question. Was there any relationship

between the development of urinary retention or other side effects on the volume or frequency of injections?

DR. SNYDER: I am going to defer that to Tina.

MS. PETERSON: We are going to do two more slides and then we will get into the questions and answers. I will be brief.

DR. A. KALLOO: Sure.

**Concluding Remarks**

**Karen Peterson, M.S.**

MS. PETERSON: Final two slides coming up here.

[Slide.]

The objectives of the clinical study have been successfully met.

This includes the evaluation of the two primary efficacy endpoints, which were improvement in continence grade and pad weight a 12 months post-treatment. Both continence grade and pad weight were significantly improved from baseline to follow-up for Durasphere patients, and the results are found to be equivalent to that of the control group.

For the primary safety endpoint, few differences were found between Durasphere patients and the control group patients in the severity, incidence, duration, and resolution of all adverse events. No new or unique safety issues were identified for Durasphere.

No significant differences were found between the

Durasphere patients and the control group patients in any of the secondary endpoints at any of the follow-up intervals.

Lastly, the durability of improvement for Durasphere was found to be not significantly different from that of the control group, however, the results are suggestive of potential longer term durability of Durasphere compared to the control material.

[Slide.]

The following conclusions from the study have been drawn:

1. Durasphere injection is safe to use for treating the symptoms of stress urinary incontinence. No safety issues arose that limit its application when used according to its instructions for use.

2. Durasphere injection has been effective in reducing stress urinary incontinence as measured by improvement in continence grades, pad weight tests, incontinence episodes, and validated Quality of Life instruments.

3. The effectiveness of Durasphere was found to be equivalent to that of the commercially available control device in a prospective, controlled, randomized clinical trial.

This study has demonstrated the safety and effectiveness of Durasphere in the treatment of stress urinary incontinence due to ISD.

I thank you very much for your attention.

DR. A. KALLOO: I had a specific question. Any questions from the panel? The question I had, was there a relationship between side effects, specifically, urinary retention and the volume or frequency of injections?

MS. PETERSON: We looked at that, and there is no relationship between those two.

DR. STEINBACH: Question. How much of the bulk was due to the pyrolytic graphite at the day of injection or the instant of injection and at long-term follow-up, because the handout we read said that most of the bulk is being provided by tissue reaction rather than the pyrolytic graphite itself? I may have misread the handout.

DR. SNYDER: If I can repeat your question, you want to know, the bulking effect, how much was due to the actual pyrolytic beads as opposed to the transfer agent beta-glucan?

DR. STEINBACH: Right.

DR. SNYDER: The percentage of pyrolytic beads that is infiltrated in the beta-glucan is right now proprietary information, and I am sure will be opened up later on.

DR. STEINBACH: It might take studies that you couldn't do in people to know how much is pyrolytic and how much is tissue material at 12 months, or is that also proprietary?

DR. SNYDER: No, I don't believe so. I think that is an excellent comment, and I think that information actually will be available at some point in the very near future in laboratory

animals.

DR. DIAMOND: I think that is a very good question. I read that also. I thought the reason that you have the bulking was collagen growth stimulated by beta- glucan, and some of what I read talked about how beta-glucan is also used in wound healing, but again, from the presentation, what I heard was that the bulking is due to the particles.

So, I think a question of which it is, is important, particularly if you deal with issues of durability and why it is there and why repeated injections might have been necessary if it is due, in fact, to the particles.

DR. SNYDER: Well, I don't believe that one can absolutely say, there is clearly no data to say that it is the particles versus the transfer agent, the beta-glucan, that is providing the bulking. I think it is probably safe to say at this point, with the science that we have, that it is a combination of both agents and possibly the reduction in the effectiveness following one injection may very well be due to absorption of beta-glucan.

DR. VERTUNO: Do you have an explanation for the increased incidence of short-term urinary retention compared to control?

DR. SNYDER: We looked at those issues because clearly, there was a difference in those 2 out of 31 groups. There were certain things that we looked at. We looked at

anesthetic agents, first of all. A variety of anesthetic agents were utilized during the procedure from local anesthesia with lidocaine, lidocaine with epinephrine, up to a more invasive general anesthetic. That analysis showed no difference between anesthetic agent and the incidence of urinary retention.

We do feel that possibly some of the incidence of urinary retention was due to the size of the needle, which is larger in the Durasphere group than the control, the technique which takes a little bit longer than the control, and irritation from the cystoscope.

DR. FOOTE: I understand through the protocol that you did follow-up urodynamics at one year. Was there a difference in the urodynamics in those patients who had experienced the prolonged urinary retention or the bladder irritative symptoms from the patients who did not?

Specifically, I am interested to know if those patients at one year demonstrated a bladder outlet obstruction.

MS. WITTCHOW: As shown on the urodynamics, we did not show evidence of bladder outlet obstruction. In this patient population, they had a lower post-void residual than our general population of patients.

DR. SNYDER: Also, interestingly, there was -- which is consistent with the majority of the literature -- there was difference in Valsalva leak point pressure of these patients, and, Dr. Foote, you had a very eloquent article back in the

mid-nineties in paraplegia, I believe, which did show some increase in Valsalva leak point pressure, but we did not show that in our population.

DR. A. KALLOO: Could the prior speaker identify herself, please.

MS. WITTCHOW: My name is Tina Wittchow, and I am the Manager of Clinical Research for the sponsor.

DR. HUNTER: Were any of the control group patients injected with periurethral, like a spinal needle, or was it all transurethral injection?

DR. SNYDER: This was purely a transurethral procedure done via the cystoscope.

DR. HUNTER: Just some clinical questions. It looks like that the gel doesn't leak out as well as the control. Is that the experience of the investigators?

DR. SNYDER: Yes. I believe that, and that is what I tried to demonstrate in the initial video. It appears that although it takes a slight bit more effort than the control to implant the device, one of the advantages is there is also a decrease in the leakage rate post-treatment.

Another observation that we made is something called urethral molding. Following the implantation of the control group, if you were to catheterize the patient, you tighten up the bladder neck in a very nice fashion with the control, but when you catheterize the patient, and you look back in with the

cystoscope, you see that the area has opened up slightly, there is a little bit of molding. It's a softer material.

With the Durasphere implant, we did not find that molding present at all.

DR. HUNTER: One investigator showed you can actually aspirate the material out?

DR. SNYDER: This is a one-site, one-patient treatment of what the investigator felt might possibly have been an abscess causing urinary retention, and this was done through a transvaginal route, aspirate of 2 ml. This is certainly not something that we recommend on a routine basis for patients.

DR. HUNTER: Did anyone experience rupture of the submucosal bleb with either the control or the Durasphere?

DR. SNYDER: Yes, I think it is fair to say that that occurs somewhat frequently depending upon the depth and volume of implant that you put in no matter what type of injectable you use, and I think the basic tenet would be to go to another area that will capture the implant.

DR. HUNTER: So, your study included the rupture because -- well, they just kept track of the total, and they just put in whatever it took?

DR. SNYDER: Yes, absolutely.

DR. A. KALLOO: What were the indications for repeat injections, how did you decide which patients you were going to do a second and a third injection?

DR. SNYDER: At follow-up visit, the patients were seen by the study coordinators and the blinded physician. The normal parameters of quality of life and incontinence pad weight tests in all the follow-ups, that were standard in the protocol, were measured.

It was then determined based upon the patient's desire and these tests, a discussion was made with these people to decide who would be re-treated.

DR. HUNTER: Would you inject the material routinely without doing a skin test? That is an open-ended question.

DR. SNYDER: Are you talking about future use?

DR. HUNTER: Yes.

DR. SNYDER: Yes, we saw absolutely no antigenicity or this implant, and were quite impressed by it, and I think this is a major advantage.

DR. N. KALLOO: Did you exclude patients with cystoceles or any other gross visible signs?

DR. SNYDER: According to the protocol, we did not include patients with Grade 4 cystoceles or significant cystoceles that were contributory to obstruction. So, patients in the population did have Grade 1's, maybe Grade 2 cystoceles, and Grade 3's and 4's were eliminated.

DR. N. KALLOO: Were there any cures? I note that you mentioned greater than one continence grade. What was your absolute cure rate with absolute dryness?

DR. BENNETT: It was on one of the slides.

MS. PETERSON: Right.

DR. BENNETT: Between 20 and 25 percent, the same in both groups.

MS. PETERSON: It was roughly a third at 12 months. Turn to page 36 of your clinical reports. It is there.

DR. STEINBACH: I noticed two of the slides you showed to the public with pad weight and with injection volume, these parameters are normally tested with the t-test, and you reported the p-value by the Fisher's Exact Test on your slide. It's not that way in the handout.

DR. HOLCOMB: There were, as you rightly assert, most of these tests of continuous measures were Student t-tests unless there was some reason not to, example, non-normal distribution of the data, but we had quite a large sample size, so that wasn't an issue for us.

There were cases where there was classification of patients, for example, in terms of severity of incontinence or whenever, where it was appropriate.

DR. STEINBACH: Could it be a typo?

MS. PETERSON: The pad weight, we used a two-sided Student's t-test.

DR. STEINBACH: It wasn't that way on the slide.

MS. PETERSON: Okay. If you look on page 38 of your report.

DR. A. KALLOO: Could you tell us the data on the male patients?

DR. SNYDER: I am sorry. Could you repeat that?

DR. N. KALLOO: Your results on male patients.

DR. SNYDER: Once again, it should be obvious that our male population was quite small.

MS. PETERSON: That was included in your appendices on the males. We do acknowledge that there was a small sample size for the males, however, some males did benefit, and there were no safety issues.

So, what we have done is in our labeling, we have acknowledged that and we have a precaution statement that reads like this: "The improvements in the male patients experience were less than that of the females, but similar to that of the commercially available control device." We have that as a precautionary statement.

DR. A. KALLOO: And the incidence of adverse effects in the males, were they any different even though it's a small group?

MS. PETERSON: It's a very small group, and it is your appendix, but you will see it is actually very comparable to the females, if not less. So, there were no new or safety issues there.

DR. HAWES: What did you learn from the repeat injections when you went in to repeat the injection, what was

the appearance, and can you derive any information of why the repeat injections failed?

The second question is did you reinspect anybody, not just urodynamics, but actually reinspect anybody at the end of the study period to look morphologically at what the injection looked like?

DR. SNYDER: To answer your first question, which was what were the observations of the clinical implanters on reinjection, I think similar findings that we found with the control group, which were there were several areas of mucosal erosion where there was some denuded mucosa, where a blebbed area of a mass had actually just busted open and been excreted out in the urine.

In none of my patients -- and I injected 34 primary patients, I had a total of 70 patients of Durasphere and controls -- did we find any beads left in the bladder in any patients, which actually surprised me a little bit. I was concerned that maybe some beads would be left in the bladder, and this was never reported by any of the investigators.

In other areas, we found the beads to be present embedded in the submucosa with some effect, but there appeared to be, one of the observations I made at termination of primary treatment was what percentage of the urethra did I close off, did I get 80 percent, 100 percent, and at reinjection, there appeared to be no correlation between the degree of closure that

we made versus the degree of continence.

So, in some patients that we got an 80 percent closure of the urethra, who we anticipated would probably need another injection, when we looked at the data, we saw that some of those patients were quite dry, and other patients where we had had 100 percent closure, at three months, six months, 12 months, those patients required reinjection.

As far as the second question -- does that adequately answer your first one?

DR. HAWES: Yes.

DR. SNYDER: As far as the second question, all patients at all follow-up visits underwent routine examination, and there were no morphologic problems that were visualized on vaginal pelvic examination.

DR. HAWES: But they didn't undergo re-cystoscopy.

DR. SNYDER: Patients did not routinely undergo cystoscopy on follow-up evaluations.

DR. DONATUCCI: Were all the episodes or urinary tract infection simple cystitis, or did any patient have an upper tract infection?

MS. PETERSON: Tina, do you want to answer that?

MS. WITTCHOW: All the events of urinary tract infection were simple cystitis. I can give you some specifics as to the urinary tract infections and the ability to resolve the infections. For our patient population, 88 percent of those

UTIs were cured with one treatment of antibiotics or one course of antibiotics, leaving about 8 percent that needed to use two courses of antibiotics to cure, usually a switch in the type of antibiotic that was being used, and 4 percent of the patient population had UTIs resolved on their own, either because the patient chose not to take antibiotics or chose to use other methods like increase their fluid, changed their practices to see if they could resolve it on their own.

So, they were fairly routine in the cure rate or resolution of those UTIs.

DR. A. KALLOO: Ms. Newman.

MS. NEWMAN: I have two questions for you. You said that your primary outcome variables have been change in continence grade and pad weight, but you said your reinjection criteria was quality of life.

Were those the same variables you looked at for reinjecting women?

MS. WITTCHOW: Reinjection, to reiterate what Dr. Snyder had said previously, reinjection was considered after an entire follow-up. For instance, the criteria for a follow-up would have been evaluating the continence status, doing a pad weight, doing a quality of life only after six and 12 month follow-up, doing a diary, and then evaluating all of those in coming up with Stamey continence grade, as well as discussing the need for re-treatment. So, all of those factors were taken

into consideration for re-treatment.

MS. NEWMAN: The second question I have is you have data on 18 months. What numbers do you have longer term, what numbers as far as reinjection rate, how many women you have long term, after 18 months, and what are you doing with that?

MS. PETERSON: So, are you asking after 18 months, how many?

MS. NEWMAN: What numbers you have on that, and how long out are there?

MS. PETERSON: Right now we have about 30, a little over 30 in each group, so about 65 patients that have hit their 18 month in the report.

MS. NEWMAN: No, but I mean beyond 18 now.

MS. WITTCHOW: We have about 30 patients at the 24-month follow-up, as well as about 9 more at the 30-month follow-up, and we have been, while the study has been open, we continue to follow them every six months.

MS. NEWMAN: Do you have data beyond 18 months then? Do you have data beyond those 18 months in a certain cohort?

DR. SNYDER: That data is currently being collected, but has not analyzed for purposes of this talk today.

DR. N. KALLOO: Were you doing any ultrasound evaluation for volume of post-void residuals?

DR. SNYDER: The standard BVI ultrasound or catheterization were the standards by which sites used for

measuring post-void residual.

DR. N. KALLOO: Were you able to see the spheres on ultrasound, did they have a typical pattern on ultrasound?

DR. SNYDER: My personal experience was that, number one, I didn't do the follow-ups because I was a blinded physician, but there was no mention of that on the ultrasound, but remember, this is not high-resolution ultrasound.

DR. N. KALLOO: Like a bladder scanner?

DR. SNYDER: This was a bladder scanner, yes, and my guess is, is that had one done intravaginal ultrasound with a high resolution, 5 megahertz or so, that you would have seen the particles.

DR. N. KALLOO: My concern would be certainly in a male, for example, who still has his prostate in, how would that patient be monitored? Were you able to feel any difference on digital rectal exam in males?

DR. SNYDER: In my site, we had no non-post-prostatectomy males, no TUR males who participated in the study. In fact, we had no male patients in my study at all, my site, so I can't answer that question.

DR. N. KALLOO: Is there anybody that can answer that?

MS. WITTCHOW: The inclusion criteria for our protocol required the male patients to be post-prostatectomy, so we did not have any males in the study that still had their

prostate.

DR. SNYDER: So, TUR incontinence after a benign prostate operation would not be a part of that cohort.

DR. N. KALLOO: I am thinking in terms of sort of spinal cord injury patients or neurologic etiologies.

DR. SNYDER: Neurologically impaired patients were excluded from the study.

DR. DONATUCCI: Pardon me if you have already answered this, but there was a statistically significant difference between the time to first re-treat and between Durasphere and the control, at least as I read it in the handout.

Was there any anatomic differences between the two groups when you looked inside for the first re-treatment?

DR. SNYDER: Dr. Donatucci, can you just tell me what -- rephrase your question again?

DR. DONATUCCI: I am referring specifically, let me find it for you --

DR. HOLCOMB: Is that Table 33 on 45?

DR. DONATUCCI: No, actually, there is another table a little later. Yes, I am sorry, it is 33 on 45, I was looking at the wrong table, exactly. The time to first and second injection was statistically different between the two groups, and I am just asking whether there was anything you found at the time. That just struck me, and I was wondering what that was.

DR. SNYDER: I don't believe so. I believe what this represents is a scheduling factor between the follow-up visit and when the -- there was no defined time period when the patients had to be injected following that evaluation, so many times patients couldn't come in during certain months of the year or at certain vacations, and so certain patients were just put off for several weeks.

DR. DONATUCCI: Artifactual then.

DR. SNYDER: I think they are artifactual, yes.

DR. A. KALLOO: Was there a difference in the quality of life scores between the two groups? I saw your zero in one year, but compared to the two groups, was there a difference?

DR. HOLCOMB: No, there wasn't, not any of the follow-ups, and not at the 12-month follow-up between the two groups.

DR. A. KALLOO: Is that surprising given the fact that the urinary retention, et cetera, was higher?

DR. HOLCOMB: I don't know if it's surprising. It probably reflects the fact that those didn't impact significantly on the people's feelings.

DR. SNYDER: I think when you look at the quality of life issues, it all is based upon or much of it is based upon the expectations of the individual patient and how much improvement that individual expects to make to be happy, and for some patients, completely dry would be the only acceptable

result, and in other patients, a significant reduction in incontinence and use of pads, et cetera, would be a significant quality of life improvement.

DR. DIAMOND: I would like to go back to the tissue reaction question. Can you tell me a little bit about beta-glucan, how long it resides in the body, how it is cleared? Is there anyone that has that information?

MS. PETERSON: Sure. I would like to have Dr. Kirkemo answer that.

DR. A. KALLOO: If you could please introduce yourself.

DR. KIRKEMO: My name is Aaron Kirkemo. I am a urologist in private practice in St. Paul, Minnesota.

The beta-glucan, we do not have an enzyme in our body, a glucanase enzyme to digest it, so if you look at the histologic data from the animals, what happens is this material is phagocytized, and you ultimately just see it sitting in macrophages and histiocytes. It is just kind of encapsulated as a foreign body.

The thing that is interesting, if you kind of look at the tissue reaction over time, it looks very bland within a very short period of time.

DR. DIAMOND: What is the time portion over which it is phagocytized? Are we talking days or --

DR. KIRKEMO: If you look at the basic response at

least from the animal models, at seven days there is a bit of an acute inflammatory response with both polymorphonuclear leukocytes -- with both leukocytes and lymphocytes.

If you look at the three-month data, by that time point it is basically early deposition of collagen, mostly histiocytes and a few macrophages, and by the time you get out to six months it's basically just bland collagen. It looks very benign.

DR. DIAMOND: So, at three months or six months is there any beta-glucan that is not yet phagocytized?

DR. KIRKEMO: I can't say exactly. At least with all the histology that I looked at, everything looked incorporated.

DR. A. KALLOO: Could you state your financial interest, please.

DR. KIRKEMO: I am a consultant for them.

DR. DIAMOND: Going back to the questions I was asking earlier, then, about what is it that is providing the durability, the comments, if it is gone pretty much at three to six months, then, it is probably the particles where collagen that develops, that is, what is acting is it is not something that at least components of the device are not persistent.

MS. PETERSON: And I think you are precisely right, it's a combination of what you just said.

DR. SNYDER: And the pyrolytic beads obviously composing --

DR. KIRKEMO: You see a volume of beads, and you see mature collagen.

DR. DIAMOND: So, what then happens in those patients who have continence or who get some improvement in a month, but don't have improvement six months, a year, 18 months in the data that were presented to us?

DR. SNYDER: Clearly, that is a multifactorial type of problem that may relate to changes in bladder function, maybe not seen initially at one month, but certainly at six months down the line, you can change the compliance of the bladder, create some de novo urgency.

You can see disruption of the bleb and loss of the implant, as you can with the control.

DR. DIAMOND: But the changes in the bladder, you should have picked up on urodynamics. Did you see differences like that?

DR. SNYDER: Urodynamics was performed at 12 months.

DR. DIAMOND: Right, and baseline beforehand.

DR. SNYDER: We did not see --

DR. DIAMOND: So, it is not changes in bladder function then.

DR. SNYDER: No, it's not, but you are asking for a theoretical of any given patient, what could potentially be the cause, and what I am trying to say is that it may be loss of implant bulk, it may be changes in the urethra, or it may be

other factors, such as pelvic relaxation that we don't measure it is difficult to measure.

Clearly, there are multiple factors that could cause that.

DR. DIAMOND: I was trying to be more than theoretical in that part of the presentation described the product as non-absorbable, and looking at the data over time, 7.3.5, it looks like continence decreases actually. Now, whether it is significant, I don't know, because I don't think that analysis was done. Section 7.3.5. I am sorry, that's not right. I am sorry, it's Table 19. I was looking at the wrong place.

Analysis has been done there, comparing Durasphere with control, but if you look at continence grade, you have greater improvement in continence grade early on than you do later on. At one month it is 1.1, and at 12 months and 18 months it is about 0.9, so you have about a 20 percent reduction in continence grade from one month to 12 months.

DR. SNYDER: Yes, and it seems to be similar in the control group, as well, and I once again would propose that the mechanisms are not completely understood. We do acknowledge that there is a decrease in continence grade, and there is some loss in continence control that is gained on initial injection that clearly happens over time. We do lose some.

DR. A. KALLOO: What I would like to propose -- do

you have a question?

DR. N. KALLOO: I do. I actually have two questions. Did you notice any granulomas in the area of the injection?

DR. SNYDER: No.

DR. KIRKEMO: No. It was very interesting that there really were not giant cell granulomas, granulomas like you might see with lipid or something like that. It was quite remarkable to me there was basically just bland collagen within a period of about three months on.

DR. N. KALLOO: The other question that I had is I noticed on your movie, on the video portion, you saw some of the beads actually come out. You mentioned that the glucan didn't come out, but I actually saw beads that came out, and my concern would be these are biodegradable, is that correct, the beads themselves, the spheres, the carbon-coated spheres?

DR. KIRKEMO: Correct, they are not biodegradable.

DR. N. KALLOO: How would you go about monitoring that, for example, over time, if those came out into the urethra and sort of stuck around in that area, over time that might set up a chronic reaction, and we know that the tissue in that area was chronic reaction. Certainly, we are concerned about things like squamous cell and that over time.

So, my concern would be how would that be monitored over time - or stone formation, for example?

DR. SNYDER: Sure. I think that is a very thoughtful

question. As I made a comment before, where I was really surprised that we didn't run into problems was in the bladder, that the dependent position of a bladder with a mild Grade 1 cystocele, that one might see beads in the bladder. At no point in any of the sites in any of the patients was there free retention of carbon particles of beads either in the urethra or in the bladder.

These beads are small enough that they get excreted out with voiding, and the patients would report that they had some sand, because to the naked eye it looks like sand, when they voided, and they looked in the toilet.

DR. KIRKEMO: And then also from the standpoint of kind of a chronic inflammatory sort of reaction, again, what was seen is you would see macrophages kind of wrap around the thing, an early granuloma formation, but then by six months all the inflammatory cells were gone, and all you would see would be a bead with just mature collagen around it, and no signs of any chronic inflammatory process going on whatsoever.

So, there was really no appearance of any chronic foreign body reaction, you know, seen within a very short period of time.

DR. SNYDER: And on follow-up, it is fair to say that when one looked back into a urethra that had been implanted for a secondary procedure, both the Durasphere group and the control group showed amazingly well-healed urethral mucosa except in the

areas that had recently burst blebs, and you saw some fraying of the mucosal tissue.

DR. KIRKEMO: And that is a phenomenon you see with any bulking agent. If the mucosa becomes disrupted, you will see sort of a roughened area.

DR. A. KALLOO: One final question.

DR. FOOTE: One quick question, and it kind of goes back to the discussion before about why some patients got better than others. Did you look back in your demographic data of your initial groups to see if there were some things in terms of demographics, in terms of what patients did better than others?

DR. SNYDER: Sure. Would you address that?

MS. PETERSON: We did a logistic regression analysis, and Rich will give you the result, and it is actually in your book, as well.

DR. HOLCOMB: Dr. Foote, it's in Appendix A of the panel pack that was presented, and we obviously were interested in identifying which patients would tend to do better than others, and as part of that, we did a multivariable analysis and identified actually five baseline factors that were associated with better success, and the details of that analysis is presented there, but it's those things that you would expect - people with worse incontinence, that was a predictor for how well they did.

DR. A. KALLOO: One very last question.

DR. HAWES: For a rather ignorant gastroenterologist, put things into a little bit of perspective for me. The average age of these individuals was 57 years old. You have provided us data that looks good for 12 months.

What happens to these people long term? I mean do you anticipate needing to reinject all these people after two years? If you do reinject them, is there just fibrous tissue, so you can't enter that subcutaneous space any longer?

It seems to me that this whole area of injection for incontinence begs for more long-term studies, and I am wondering what your perspective is on that. I know your data just addresses 12 months, but to me, as I assess this as a treatment for patients, it seems to me that a longer term perspective needs to be provided.

DR. HOLCOMB: Let me just address maybe two subpoints. First of all, with regard to effective age of patient, that did not turn out to be a predictor for success in the study, so younger patients and older patients had similar success profiles.

DR. HAWES: For 12 months.

DR. HOLCOMB: For 12 months. Actually, the data in the tables, for example, Table 19, that was referred to earlier, goes out to 18 months, and after that initial decline after the first month, to date -- and, of course, you are always limited by how far that you look out -- but to date, it looks like we

have a relatively stable performance profile for patients out to 18 months and the 24 months, the initial data there suggests that, as well.

So, you can't say what will happen in five years, but certainly the data we have to date suggests that you have got a stable persistent response with the Durasphere patients.

DR. SNYDER: I think based upon previous intra-urethral implant bulking agents, such as teflon and Contigen, we don't typically see fibrosis. It would be a very unusual thing to see in the urethra looking out beyond a year.

The potential of this device, the advantages besides the decrease and immunogenic nature of it, is the fact that the carbon beads may stay long enough to give a longer lasting result, and that is yet to be determined, but as Rich just stated, at 18 months it look like there is some durability at this point, but this is stopping the clock at one moment, and we will have to see.

DR. A. KALLOO: We will now take a short, 10-minute break and reconvene promptly at 11:20.

[Recess.]

DR. A. KALLOO: If I could have everyone please take their seats.

The meeting will now reconvene with an open committee discussion. Dr. Jenelle E. Foote will give a clinical overview of incontinence.

Dr. Foote.

**Clinical Overview of Incontinence**

**Jenelle E. Foote, M.D.**

DR. FOOTE: I am very happy to be here. I appreciate this opportunity to address the panel and address guests, and I felt that today it would be important to put the current discussions in the framework of the work that has been done on incontinence of all sorts, not just stress incontinence, and so what I have prepared for this morning is a review of the evaluation and treatment of urinary incontinence in the female.

[Slide.]

As was mentioned earlier, urinary incontinence is a big problem affecting about 13 million Americans, most of which are women. A quarter of these women are in this age group, and incontinence affects 50 percent of the elderly.

[Slide.]

There are implications in regard to incontinence to include emotional problems, social activity, skin problems, as well as cost, and this cost is not only in terms of medical treatment, that that individual may get from a physician or from a hospital or another health care provider, but also in the use of pads and padding and bedding that need to be changed to deal with this problem.

[Slide.]

Incontinence occurs because there is problems in

regards to the storage of urine and urinary tract, specifically, the lower urinary tract, the bladder and urethra.

[Slide.]

If you can remember this little summary here, this will help you understand many of the times when urologists discuss continence, remember that is a function of normal bladder function plus normal sphincteric function. You need to have both of them working well to allow for continence.

[Slide.]

Keep in mind also that the neurologic control over the lower urinary tract is essential to allow for continence, hence, the problems with continence in individuals who have neurogenic problems.

[Slide.]

In terms of the etiologies, including neurogenic etiologies, trauma either from surgery or obstetrical trauma, as well as certain congenital conditions and hormonal conditions, can be associated with incontinence.

[Slide.]

In regards to the diagnosis, the workup for the typical urologist or other health care provider evaluating incontinence, a good history, as well as a physical examination is necessary, a urinalysis with a culture and sensitivity being done if there is worry of infection, with urodynamics being the functional test that is done in many cases to help determine the

type of incontinence and so guide therapy.

[Slide.]

There are four basic types of incontinence, and I show this slide to illustrate that there is overlap, and so the evaluation of a patient with incontinence can be quite complex as you can have a patient with more than one type. I am going to be talking specifically this morning about urge incontinence, then briefly about overflow incontinence, and lastly, stress incontinence.

I am not going to specifically talk about functional incontinence, but suffice as to say that functional incontinence is associated with individuals who have problems with the habit of toileting. This includes individuals who have physical disabilities, as well as cognitive disabilities that make toileting difficult.

[Slide.]

In regard to urgency incontinence, this woman's face says it all. Essentially, an overactive bladder is acting without the owner's permission, if you will, and contracting, allowing for the expulsion of urine. If the external sphincter is not competent enough to prevent the flow of urine, if the external sphincter is tight enough to prevent the leakage of urine, the individual can experience suprapubic discomfort, as well as pain and a feeling or urgency.

[Slide.]

These patients can be characterized as having the so-called overactive bladder. When you see this term, this refers to a situation where the individual experiences these symptoms without any known neurologic or metabolic cause.

[Slide.]

In terms of the treatment for the overactive bladder or to instability or to hyperreflexia, there is a lot of different terms that you will see used for this. Another term is hypertonic bladder. They include the use of pads, of course, behavioral modification, pharmacologic therapy is the mainstay of therapy in 1999. Also, used is electrostimulation, as well as a variety of other surgical treatments.

[Slide.]

As I mentioned before, drugs are the mainstay of therapy. These drugs tend to be anticholinergic and a spasmodic in character.

[Slide.]

The three main generically available drugs are seen here. In the last two or three years, we have seen a number of other drugs that have been recently developed to cut down on the side effects associated with these drugs, which are predominantly anticholinergic. These patients many times have a dry mouth and constipation.

One of the newer treatments for urgency and urgency incontinence is use of sacral nerve stimulation, and as Mr. St.

Pierre talked earlier, this procedure was recently approved.

[Slide.]

This form of therapy allows for stimulation of the pelvic nerves that go to the pelvic floor.

[Slide.]

Via the S3 nerve, and in doing so, affects incontinence.

[Slide.]

The next type of incontinence I would like to review if called overflow incontinence. In contrast to the previous type of incontinence, this incontinence is characterized by a bladder that can't empty either because there is some element of obstruction at the level of the bladder neck or that the bladder has lost its tone and does not push adequately to empty.

Essentially, what empties out in this individual is the amount of urine that exceeds the capacity of the bladder, hence, the word overflow.

[Slide.]

In this condition, this is seen not uncommonly in long-standing diabetes, as well as certain neurogenic dysfunction, and in able-bodied individuals, bladder habits that delay voiding, the so-called nurses' bladder.

[Slide.]

Treatments for this include bladder training, not exactly as you see here, but basically, the individual is taught

or prompted to void on a regular basis.

[Slide.]

Timed voiding for patients who are not cognitively impaired by teaching the patient to go by their watches, of how they feel, can be very useful for this disorder.

[Slide.]

And for individuals who cannot empty despite those types of programs, catheterization is the preferred method of treatment.

[Slide.]

Stress incontinence is the type of leakage that we think about when we think about stressful maneuvers like in this little cartoon, the woman lifting the groceries out of the back of a car, coughing, sneezing, laughing, jumping, there is pressure from the abdominal muscles that is exerted on the bladder. If the bladder is full, and the bladder neck or supportive structures are incompetent, there can be leakage of urine.

[Slide.]

In this condition, generally, the individual reports small losses of urine when doing these so-called stressful maneuvers, and typically, the individual is dry at night or when they are not engaged in stressful maneuvers.

[Slide.]

In regards to the evaluation of stress incontinence,

one is concerned about how much pressure it takes to open up the bladder neck, and this has been described a number of ways. Closure pressure has been used to quantify this, as well as leak point pressure.

[Slide.]

In terms of the treatments, the include pelvic floor exercise training, use of prostheses, and what I call the patches and the plugs, as well as various surgical options, and we are going to go over those briefly.

[Slide.]

The use of pelvic floor exercises is recommended, and I certainly recommend it for the primary treatment in most women presenting to me who have stress incontinence, because you may not need to do this if the person can strengthen the pelvic floor and decrease incidents of incontinence.

[Slide.]

These so-called Kegel exercises have been rejuvenated and --

[Slide.]

-- are being done with a variety of aids to make them more effective. This, for example, is the use of a type of weighted cone that I call barbells for the pelvic floor, that can be used to help make these pelvic floor exercises more effective.

[Slide.]

In addition, the use of biofeedback and electrostimulation can also make these exercises more effective.

[Slide.]

There have been a number of studies looking at the benefit of electrostimulation for the treatment of incontinence. If you look here under stress incontinence, although the success rate in regards to cure is moderate, there is a variety of improvement rates that run the gamut from 20 to 100 percent.

[Slide.]

As regards to certain patches and plugs, I have a couple of them here that I am showing to you, that are not commercially available right now. The panel may be hearing about some in the future. I do know that there are some in commercial development.

[Slide.]

The purpose of these devices is to stem the flow of urine by using a device either inserted in the vagina or in the urethra to effect continence.

[Slide.]

Next, I would like to talk briefly about something that you may have heard about, and that is the types of stress urinary incontinence. Classically, urinary incontinence has been graded from a Type zero to a Type III. You are hearing less and less of that in the literature these days.

[Slide.]

Suffice as to say the type of incontinence that you have heard about the most often is the so-called Type III incontinence, also known in today's parlance as intrinsic sphincteric deficiency, and you heard that term discussed at the discussion earlier today.

In terms of causes of Type III stress incontinence or ISD, it includes previous pelvic surgery, radiation therapy, neurogenic dysfunction, as well as other kinds of causes to include the lack of estrogen in women who are postmenopausal.

[Slide.]

In regards to the current thinking, again, at one time we were very rigid and tried to put patients in one camp or the other, i.e., patients who have Type zero to II stress incontinence in which anatomic malposition or weakness of the pelvic floor supporting the bladder was felt to be the problem, and the other camp being that of ISD Type III incontinence or that of the dysfunctional urinary sphincter being the cause.

What we understand now is that it is more of a combination of the two in most patients, and so that we are, in terms of urologists, are changing our ways in terms of how we are approaching patients, appreciating that patients will likely have a combination of these two types of factors contributing to stress incontinence. I am talking specifically about women in this regard.

Next, in regards to the typical and classic bladder

neck suspensions that have been suggested and are still done for the treatment of Type zero through Type II stress incontinence, they are called a variety of different names. Those of you in the audience may recognize the name of some of these operations that are named after surgeons. Surgeons are egotistical, so they like to put their names on procedures.

[Slide.]

Just to show you what these operations try to do by restoring the anatomy of the pelvic floor. In this little cartoon, you can see a bladder here with a bladder neck and urethra here in this side view of a woman's pelvis. Note here the pubic bone and note that there is a distance in between the bladder neck and the pubic bone.

This distance is theoretically felt to be due to something called pelvic relaxation or weakness of the pelvic floor, such that the bladder neck is a fair distance away from the pubic bone.

[Slide.]

What the surgical action attempt to do is to restore this anatomy, i.e., to bring the bladder neck close to the pubic bone.

[Slide.]

What I would like today is just to briefly talk about a study that was commissioned by the AUA to look at the long-term results. There was a question, and an excellent

question, earlier today about what is the long-term benefit of these different types of technologies that are being proposed for stress incontinence, and, as urologists, we have recognized the importance of looking at long-term data.

[Slide.]

In this particular study, I am just going to highlight two slides from this study. There were two types of operations that were felt to have the best long-term success rate. In this study, they looked at a number of studies in the literature that were felt to be good studies, that had some objective measures for inclusion, their criteria, as well as success, and they found that the retropubic suspensions, known as the MMK's, the Birch procedures, as well as the Richardson repairs, were felt to have fairly good long-term success rates, about 90 percent going at greater than 48 months.

[Slide.]

For those non-surgeons in the audience, what these operations do is to bring the bladder neck close to the pubic bone, as I mentioned earlier. This is a picture showing a Birch procedure with the foot of the patient being here, the head of the patient being here. Here is the bladder, here is some fascia on either side of the bladder that is being sutured up to this ligament on either side of the pelvis, so-called Cooper's ligament.

You can see that the bladder is being suspended by

this fascia and therefore, the bladder neck is being brought close to the pubic bone.

[Slide.]

On the side view you can see a little bit more dramatically in this cartoon how that is represented.

[Slide.]

In the next category of this study that showed the procedure having the best long-term success rates was that of the so-called sling procedure, and at 48 months you can see this procedure had a median of probability of cure, dry or improved, of 87 percent.

[Slide.]

In this particular operation, a piece of fascia or other material is placed underneath the bladder neck with the purpose of lifting the bladder neck in addition to restoring the anatomic proximity of the bladder neck to the pubic bone, also giving some coaptation of the bladder neck area and proximal urethra.

[Slide.]

The artificial urinary sphincter is a device that has been popularized for the treatment of stress incontinence or ISD. It is used mostly in men. In women, there is a relatively high rate of erosion with these devices. As you may know, this is a hydraulic device that involves the use of fluid that is cycled through a pump device to a cuff that is placed around the

urethra that affects continence.

[Slide.]

In regards to the injections that we are discussing today, the way that those are felt to work is through a bulking action, and you saw some fairly dramatic pictures earlier in the presentation, but in this cartoon I wanted to just demonstrate that in the before picture there is non-coaptation of the bladder neck and such that the leakage or urine can be pretty significant.

[Slide.]

Where the bulking agent is used, essentially, you fill in the gap at the bladder neck and proximal urethra, thereby increasing resistance at this area and affecting continence, and as you know, there are several agents that have been tried in the past and are currently being investigated for the use of continence in these patients.

I would like to take any questions if there are any.

DR. A. KALLOO: Thank you, Dr. Foote.

DR. FOOTE: Thank you.

DR. A. KALLOO: Next, we will proceed with the FDA presentation. I would like to remind the panel that they may ask for clarification of any point included in the FDA's presentation, but the discussion should not go beyond clarification.

The first speaker for the FDA is Dr. Rao Nimmagadda.

**FDA Presentation**

**FDA Lead Reviewer**

**Rao Nimmagadda, Ph.D.**

DR. NIMMAGADDA: My name is Rao Nimmagadda. I am a chemist in the Urology and Lithotripsy Devices Branch and the Lead Reviewer for the Durasphere PMA.

My presentation is an overview of the Durasphere PMA and does not go into the details as the sponsor has already made a detailed presentation. In my presentation, I shall only outline the various aspects covered in the PMA and point out some of the issues that are still under review.

[Slide.]

The PMA was first submitted in December 1998 to document the safety and effectiveness of Durasphere, and updated in June 1999 to include additional clinical data. The PMA contains information about: the device description and how the device improves or cures incontinence, manufacturing and device specifications, preclinical testing including a two-year dog study, clinical studies, summary of safety and effectiveness, device labeling, post-approval study proposal.

Let me now briefly discuss each section to draw your attention to some important points and issues.

[Slide.]

Durasphere is a sterile, nonpyrogenic, injectable bulking agent composed of pyrolytic carbon-coated zirconium

oxide beads suspended in an aqueous beta-glucan carrier gel. The pyrolytic carbon-coated beads have a size range of 212 to 500 microns. The carrier gel is approximately 97 percent water and 2.8 percent in beta-glucan.

When Durasphere is injected submucosally in the periurethral tissue at the bladder neck, it increases the tissue bulk and produces coaptation of the bladder neck and/or urethra. By increasing urethral resistance to urine flow, this coaptation reduces and in some cases even eliminates urine leakage.

Durasphere is formulated Advanced UroScience from the components, pyrolytic carbon-coated zirconium oxide beads and beta-glucan powder received from the vendors.

The sponsors prepares the beta-glucan gel, adds the pyrolytic carbon-coated beads to the gel to produce the desired concentration of the beads, fills 1 ml syringes with the material, packages each syringe and steam sterilizes the packages.

[Slide.]

The manufacturing of the pyrolytic carbon-coated zirconium oxide beads reproducibly according to specifications (212 to 500 micron size range) to ensure the absence of small particles below 80 microns by sieving the beads and removing carbon soot on the beads by washing and to ensure the purity of beta-glucan gel is critical for the safety of Durasphere.

If there are particles below 80 microns in Durasphere, they may migrate to distant sites, such as liver, kidney, and lung, and cause serious complications. If beta-glucan has higher levels, that is, greater than 2.5 percent of impurities such as protein, it may increase the risk of sensitization reaction in patients.

The carbon-coated beads account for a specific percentage of Durasphere's volume and the sponsor maintains the bead concentration within narrow limits. If the beads occupy less than the specified volume, the bulking effect per ml of Durasphere would be less than that found in the clinical study.

Since Durasphere is a permanent implant, it has to be sterile and nonpyrogenic. The firm's manufacturing procedure is designed to ensure conformance to these specifications.

[Slide.]

Biocompatibility testing. The firm had conducted both short-term and long-term biocompatibility studies. The short-term studies include: pyrogenicity, Guinea pig sensitization, cytotoxicity, systemic toxicity, hemolysis, muscle implantation (45 days) and Ames mutagenicity tests.

These tests showed that Durasphere is not toxic. Other tests include 7-day and 28-day dog studies, as well as a 2-year dog study, in which Durasphere was injected in the periurethral tissue.

The injection sites revealed mild to moderate

granulomatous inflammation/subacute inflammation in the 7-day dog study and trace to mild granulomatous inflammation in the 28-day dog study.

Dr. Herrera will address a possible consequence of this inflammation in his presentation. After this initial phase, the tissue response from the carbon-coated zirconium oxide particles was found to be a normal tissue response to the presence of foreign material.

The sponsor has adequately addressed any potential concerns regarding the migration of carbon-coated beads to distant sites and organs, providing reasonable assurance of the safety of these beads.

The clinical section covers various topics: study objectives, study design, study protocol, description of patient population, effectiveness and safety results, summary and conclusion.

You may remember from the sponsor's presentation that a total of 578 patients were tested for skin sensitivity at 9 U.S. sites and 1 foreign site, and 355 were treated. All of these patients I am referring to here are female patients, and my presentation discusses the study results only on females, because there were very few males.

Eighty percent of the patients treated are Caucasian and 19 percent of the patients are Hispanic, primarily from the Costa Rican site. Afro-Americans accounted for only 1 percent of